High-Performance Polymers and Their Potential Application as Medical and Oral Implant Materials: A Review

Wiesli, Matthias Guido ; Özcan, Mutlu

Abstract: PURPOSE To review the literature on high-performance polymeric (HPP) materials used as medical and oral implants and make comparisons with the commonly used titanium. MATERIAL AND METHODS Original scientific articles published in English in MEDLINE (PubMed-NCBI) and Picarta literature databases between January 01, 1995 and June 01, 2013 were included in this review. Additional information was derived from scientific reports, medical and chemical textbooks, handbooks, product information, manufacturers' instructions, and Internet web sites of the manufacturers. RESULTS Based on the 7 animal studies and 1 clinical study, HPP polyetheretherketone (PEEK) consisting of a single monomer and featuring a low Young modulus may be advantageous. PEEK seems to lead to less osteolyses and healing problems and no scattering in radiation was observed. Some animal studies showed direct contact between PEEK and the bone with high biocompatibility and no evidence for cytotoxicity, mutagenicity, carcinogenicity, and immunogenicity to the present day. CONCLUSION The HPPs (ie, PEEK) may carry some potential to be an alternative material for titanium as medical and dental implants. Yet, clinical and animal studies are limited in the field of implantology with such materials.

DOI: https://doi.org/10.1097/ID.0000000000000285

Originally published at:
Wiesli, Matthias Guido; Özcan, Mutlu (2015). High-Performance Polymers and Their Potential Application as Medical and Oral Implant Materials: A Review. Implant Dentistry, 24(4):448-57.
DOI: https://doi.org/10.1097/ID.0000000000000285

High-Performance Polymers and Their Potential Application as Medical and Oral Implant Materials: A Review

Matthias Guido Wiesli, MD, MDent Med,* and Mutlu Özcan, DDS, DMD, PhD†

Purpose: *To review the literature on high-performance polymeric (HPP) materials used as medical and oral implants and make comparisons with the commonly used titanium.*

Material and Methods: *Original scientific articles published in English in MEDLINE (PubMed-NCBI) and Picarta literature databases between January 01, 1995 and June 01, 2013 were included in this review. Additional information was derived from scientific reports, medical and chemical textbooks, handbooks, product information, manufacturers' instructions, and Internet web sites of the manufacturers.*

Results: *Based on the 7 animal studies and 1 clinical study, HPP polyetheretherketone (PEEK) consisting of a single monomer and featuring a low Young modulus may be advantageous. PEEK seems to lead to less osteolyses and healing problems and no scattering in radiation was observed. Some animal studies showed direct contact between PEEK and the bone with high biocompatibility and no evidence for cytotoxicity, mutagenicity, carcinogenicity, and immunogenicity to the present day.*

Conclusion: *The HPPs (ie, PEEK) may carry some potential to be an alternative material for titanium as medical and dental implants. Yet, clinical and animal studies are limited in the field of implantology with such materials. (Implant Dent 2015;0:1–10)*

Key Words: biocompatibility, high-performance polymer, implantology, oral implants, osseointegration, polyetheretherketone, titanium, Young modulus

Titanium (Ti) and its alloys are broadly used as dental and orthopedic implant materials due to a combination of favorable properties, such as high corrosion resistance, biocompatibility, repassivation, and adequate mechanical properties.[1,2] Electrochemically, it is classified as base metal and has a high affinity to oxygen. The corrosion resistance of Ti and its alloys is a result of spontaneously formed passive oxide films (TiO_2) when in contact with oxygen.[3] The Ti surface will be then covered with an oxide film within nanoseconds, yielding to passivation of the metal, protecting the device made of Ti against aggressive attacks and making the surface less reactive.[4] TiO_2 is a stable and dense layer, which acts as a protective barrier to continuous metallic oxidation. This means titanium reveals a high resistance to corrosion. In the event of damage, TiO_2 has the ability to spontaneously reform under normal physiological conditions. However, events, such as cyclic loading, implant micromotion, acidic environments, and their combined effects, can result in permanent breakdown of the oxide film, which may consequently lead to exposure of the bulk metal to an electrolyte. During this process, a large amount of metal ions and debris are generated, of which their accumulation may lead to adverse tissue reactions in the oral environment.[5] Ti and its alloys as dental implant material is commonly used and seems to be safe referred to its application. In conjunction with other metals and in an aqueous environment such as the mouth cavity, the passive surface may be impaired and as a consequence lead to osteolysis.[6] This may cause potential occurrence of neoplasia by metal traces of dental implants.[7]

There are several factors that influence the anchorage of implants in human bone, where bone quality, material type, form, surface texture, and chemistry play a role in a faster apposition of the bone and eventually osseointegration.[8] However, potential release of surface coating materials, such as hydroxyapatite (HA), may induce peri-implantitis.[9] Another reason for implant-borne

*Medical Doctor and Dentist, University of Zürich, Center for Dental and Oral Medicine, Zurich, Switzerland.
†Professor, Head of Dental Materials Unit, University of Zürich, Center for Dental and Oral Medicine, Clinic for Fixed and Removable Prosthodontics and Dental Materials Science, Zurich, Switzerland.

Reprint requests and correspondence to: Mutlu Özcan, DDS, DMD, PhD, Dental Materials Unit, University of Zürich, Center for Dental and Oral Medicine, Clinic for Fixed and Removable Prosthodontics and Dental Materials Science, Plattenstrasse 11, CH-8032 Zürich, Switzerland, Phone: +41-44-63-45600, Fax: +41-44-63-44305, E-mail: mutluozcan@hotmail.com

ISSN 1056-6163/15/00000-001
Implant Dentistry
Volume 0 • Number 0

DOI: 10.1097/ID.0000000000000285

infections is the development of biofilm on the Ti surface where the surface texture and physicochemical surface properties of the implant and the diminished immune-mediated response at the implant-tissue interface are held responsible. The surface protein layer, formed under physiological conditions, is essential for the biocompatibility of Ti.[10] However, this protein layer may also facilitate the colonization of microorganisms.[11] A biofilm is a cell aggregate where bacteria are adhered to each other and produce extracellular polymers. These extracellular polymers protect the microorganisms against body defence.[12] Furthermore, antibiotics could hardly destroy the biofilm,[13] meaning that an implant may need to be removed in most cases to destroy the biofilm and heal the infection.

Even though Ti and its alloys acquire many encouraging properties, corrosion happens pathophysiologically when the implant is in contact with the oral fluids. Due to this condition, Ti releases ions (ie, Ti [IV], V, and Al) and trigger an immune reaction that is potentially directed toward the implant. The reported immune reaction is part of the type IV reaction.[14] Another important issue related to the metallic implants is that their presence evokes considerable scattering rays in the field of irradiation.[15,16]

Currently, there are more than 1300 dental implant systems available on the dental market that differ in size, shape, and surface characteristics.[17] Yet, during the last 2 decades, efforts are being made to develop metal-free implants, abutments, and restorative materials. One such example is zirconium dioxide.[18,19] Unfortunately, low temperature degradation and high Young modulus are potential disadvantages of this material.[20,21]

The spectrum of applied implant materials in medicine, especially in orthopedic and traumatic surgery relied mainly on the use of cobalt-chrome alloy, stainless steel, or Ti materials by large size for pins, plates, screws, or total joints. Alternatively, individualized cobalt-chrome implants with titanium plasma spray coatings for talar and tibial or total ankle replacement were tried.[22] However, orthopedic implants presented similar problems associated with the released metal ions as experienced with oral implants. Osteolysis is a result of wear-induced particles that diffuse within the effective joint space.[23] The second-generation metal-on-metal bearing couple implants were expected to reduce the osteolysis due to wear of the implants.[24] Opposite to the expectations, metal-on-metal bearing couple implants generated higher number of smaller particles (up to 13.500 times) than a metal-on-polyethylene (PE) couple as a result of wear, corrosion, and a combination of both. To date, there is no strong evidence of a risk for carcinogenesis or teratogenesis[25] according to the level of metal ions measured in plasma using spectrometry.[26]

Nonetheless, for the above stated reasons related to the disadvantages of Ti, cobalt-chromium, and even zirconium dioxide, metal-free materials, namely high-performance polymers (HPPs), are being proposed as implant materials in medicine. So far, the most commonly used HPP is polyetheretherketone (PEEK) that was first characterized in the 1990s and belongs to the polymer family of polyaryletherketone (PAEK). Soon after its synthesis, it started to be used increasingly in orthopedic, traumatic surgery and in particular as spine implants.[27–29] From the biomechanical point of view, reinforced version of PEEK has a similar Young modulus (18 GPa) with the human cortical bone, which makes it an "isoelastic" implant material.[30] The possibility of sterilization of PEEK and no scattering under irradiation presented the material as a potential alternative to metallic implants.[27] Table 1 demonstrates an overview on the classification of commonly used polymers for medical and dental applications.

The objectives of this literature review, therefore, were to evaluate the present literature and gain insight into the newly developed HPP materials used as medical and oral implants and make comparison with the commonly used titanium. The focus in this literature review will encompass an investigation on chemical, mechanical, and biological properties of HPPs and their application particularly in medicine and dentistry as implant materials. Based on the available *in vitro*, animal and clinical studies, the performance of these synthetic materials will be compared with that of titanium. Finally, conclusions will be made whether HPPs could substitute titanium for clinical applications as an implant material or not.

MATERIALS AND METHODS

Search Strategy

Original scientific articles published in English in MEDLINE (PubMed-NCBI) and Picarta literature databases between January 01, 1995 and June 01, 2013 were included in this review. The following Medical Subject Headings (MeSH), search terms, and their combinations were used: ("Dental Implants" [Mesh]) AND ("polytetrafluoroethylene-silicone" [Supplementary Concept] OR "Polytetrafluoroethylene"), ("Polymers" [MeSH]) AND "Dental Implants, Single-Tooth" (MeSH), ("Polymethacrylic Acids" [Mesh]) AND ("Dental Implants" [MeSH] OR "Dental Implants, Single-Tooth" [MeSH]), ("Orthopedics" [MeSH]) AND ("Prostheses and Implants" [MeSH]) AND "Polymers" (MeSH), "Polymers and material and oral implant," "Fiber-reinforced composite and dental implant," "Fiber reinforced resin and oral implant," "Arthroplasty

Table 1. Classification of Major Conventional and HPPs Used for Medical and Dental Applications

Major Polymer Types	
Conventional Polymers	HPPs
Methyl methyacrylate (MMA)	PEEK
2-Hydroxyethyl methacrylate (HEMA)	Polyether ethylene glycol (PEEG)
2,2-bis[*p*-(2-hydroxy-3-methacryloxypropoxy) phenylene]propane (bis-GMA)	Polyethylene glycol (PEG)
1,6-bis(methacryloxy-2-ethoxycarbonylamino)-2,4,4-trimethylhexane (UDMA)	Bioglass
Triethylene glycol dimethacrylate (TEGDMA)	

and titanium," "PEG and dental implant," "Scattering effects and titanium implant," "High performance polymers and PAEK," "High performance polymers and PEEK," "High performance polymers and PEKK," "High performance polymers and titanium," "High performance polymers and oral implants," "PEEK and titanium," "PEEK and oral implants," "PAEK and titanium," and "PAEK and oral implants." Additional information was derived from scientific reports, medical and chemical textbooks, handbooks, product information, manufacturers' instructions, and Internet web sites of the manufacturers.

Inclusion/Exclusion Criteria

Publications only in English language, where full texts were available, including abstracts, were included. Due to the limited number of studies available, no restrictions were made on study designs. Thus, all experimental, animal, and clinical studies were included.

Data Extractions

Two independent reviewers (M.G.W. and M.Ö.) screened the material retrieved from the electronic and hand-searched articles for possible inclusion in the review. After initial elimination, based on the titles and the abstracts by both reviewers, full-text articles were obtained. In addition, hand searches were performed on bibliographies of the selected articles and identified narrative reviews to find out whether the search process has missed any relevant article.

RESULTS

Types and Chemistry of HPPs

Among HPPs, such as PEEG, PEG polysulfone, polybutylene and others, there seems to be more possibilities to create a composite with the pure PEEK biomaterial. Composite materials consist of 2 or more phases and show their own physical, bioactive, and mechanical properties. They are bonded together by an interface, and the overall mechanical properties are a combination of both materials. PEEK can be reinforced by carbon (carbon fiber–reinforced PEEK = CFR-PEEK) and glass fibers that lead to improved wear resistance and excellent mechanical properties in increased strength and stiffness.[28,31–34] Also, barium sulfate, a radiopacifier, may be added to PEEK to improve visualization and contrast in imaging. This procedure is often applied in trauma surgery.[35]

There are many monomers that are arranged in repeating units. If 2 or more monomers are used in a material, it is called copolymer. Furthermore, a polymer may not only be linear but also branched. However, PEEK comprised a chain of 100 linear monomer units with an average molecular weight of 80,000 to 120,000 g/mol. The length and the composition of the molecular chain have a strong influence on the properties on temperature resistance and deformation. There are several possibilities to control physical properties of the material. PEEK are sometimes referred as to polyetherketone (PEK) belongs to the family of polyaryletherketone (PEAK) and is a high-performance thermoplastic polymer. PEEK is a linear homopolymer, meaning that it consists of only a single monomer (Fig. 1). There are other HPPs on the market, such as polyetherketone ketone (PEKK), but PEEK is the most commonly used polymer for implants in medical application.

PEEK is synthesized by alkylation of bisphenol salt. The reaction of 4,4′-difluorobenzophenon with hydrochinon salt is extremely frequent. The presence of the aromatic rings (benzene) gives the molecule certain stiffness. Nevertheless, the ether (-o-) bond shows another property, namely, the molecule is able to rotate in an axillary direction on this position. When the molecule is slowly cooled down from the molten state, there exist 2 different microstructure phases. On one side, the folded chain gets into ordered domains (crystalline phase), and on the other side, the amorphous phase surrounds the crystals. Thermal processing can control the amount of the crystalline content. The typical quantity in implants is between 30% and 35%. Even so, it is possible to generate a near-amorphous structure by adjusting the cooling rate.

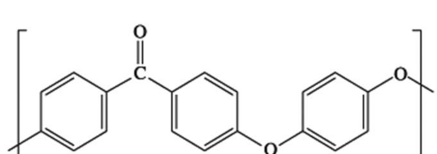

Fig. 1. Chemical formula of poly(aryl-ether-ether-ketone), commonly abbreviated as PEEK. The molecule is relatively stiff due to the presence of the aromatic (benzene) rings in its backbone. At the same time, the molecule does have the freedom to rotate axially around the esther (-O-) and ketone-carbon bonds (-CO-).

The chemical structure of PEEK presents some outstanding properties, such as resistance to chemical and radiation damage, high stability at temperatures above 300°C, and a greater strength than many metals. The possibility to reinforce PEEK with other materials, such as glass or carbon fibers, gives this polymer a special quality. However, PEEK is used in medical and dental applications not only because of its stability, biocompatibility, and mechanical properties, but also for its radiolucency. Pure PEEK has a tan color and is available as pallets or powder. If PEEK is reinforced with carbon fibers to improve strength, the color changes into black.[27–29]

Production Process of PEEK

The production of this high-performance thermoplastic polymer in medical or dental implants is a difficult process. PEEK is exceptional in its being a chemical inert material, which is very important for implants. Moreover, it is insoluble in all solvents at room temperature. The production process of the major polymer PEAK from the family of HPP is related with high costs in comparison with other thermoplastics. There are 2 different ways to manufacture PEAK. One is the electrophilic reaction where aromatic ether species are linked with ketone groups. The other route is to link the aromatic ketone with an ether bond, which is called as nucleophilic displacement reaction.[29]

Electrophilic Reaction

PEAK cannot be synthesized in usual solvents because of its natural resistance toward solubility and tendency to crystallize at a high level. The electrophilic reaction consists of protonating a carbonyl by using anhydrous hydrogen fluoride/boron trifluoride (HF/BF_3). This process leads to a high-molecular weight PEK. There are many other electrophilic reactions to produce PEAK. Later, PEAK was synthesized in a similar way with alkylthio-chloroformates (Raychem Ltd., Mumbai, India), and polycondensation of 4-(4`-phenoxyphenoxybenzoic acid) was achieved in trifluoromethanesulfonic acid. Benzoic acids are substances with reactive end groups of the electrophilic reaction. This means that such agents cannot be manufactured without end-capping in consequence of their thermal instability. The circumstance of high temperature processing would lead to cross-linking of polymers and producing gels.[27–29]

Nucleophilic Displacement Reaction

It is very important to use the appropriate solvent to synthesize PEEK due to its reduced solubility. Thermal stability and a resistance toward phenoxide species, such as benzophenone or diaphenylsulfone, is a relevant feature. However, biphenates are instable to oxidation. For that reason, biphenates are produced *in situ* by using hydroquinone and sodium or potassium carbonate. A high temperature (>300°C) is necessary to obtain a high molecular mass. This can be measured by getting an excess of difluorobenzophenone, which is formed to fluorine-terminated chain. The described method is often used in the industry and presents the ability to produce many different variants of the PEAK family, such as PEK, PEEK, PEKK, PEKEKK, and so on. The often-used polymer of the PEAK family, PEEK merges into glass at a temperature of about 143°C and presents a crystalline melt transition temperature of about 343°C.[27–29]

Young Modulus and Yield Stress of PEEK

PEEK presents different mechanical properties than metal devices, such as Ti, its alloys, and Co-Cr, because of its structure and process of production. Unfilled PEEK has a Young modulus between 3 and 4 GPa.[28,32,36] The Young modulus of PEEK can be increased from 19 to 150 GPa with additives, such as carbon fiber.[34] Table 2 shows the Young modulus of different forms of titanium, PEEK, Cr-Co, and bone.

Table 2. Young Modulus of Different Implant Materials

Material	Young Modulus (GPa)
Pure titanium	100
Ti6Al4V	110
Ti6Al4V with 23–32 vol% porosity	7–60
Chrome-cobalt	180–210
Unfilled PEEK	3–4
CFR-PEEK	19–150

Osseointegration of PEEK

Osteointegration or biocompatibility is the interaction between the biomaterial and the ambient tissue. Each tissue of the body is different. Blood makes another interaction with PEEK in comparison with bone. Pure PEEK polymers appear in a bulk form as an inert material. There is no observed adverse effect, such as releasing ions. Bioactivity means a positive interaction with tissues and leads to a differentiation of cells. PEEK is not known as a bioactive material. Nevertheless, there results a direct contact between PEEK and the human bone. Toth et al[36] showed in their study the histologic fusion between PEEK cages packed with autograft or rhBMP-2 and bone of sheep after 6 months. There was no evidence of degradation or wear debris.[36] However, there was no chemical bond between PEEK devices and bone, implying that there were only micromechanical interlocks.[36] If there evolves no histological fusion between PEEK and bone, pseudoarthrosis occurs. These phenomena caused of relative motion between the device and the bone refer to debris around the implant in tissue. The result is an inflammatory response with macrophages and other immune cells, such as lymphocytes and plasma cells, which may be followed by a chronic inflammation.[29]

PEEK was also tried to be coated with HA in an attempt to increase the cell attachment to the implant surface. Such a coating presented promising results compared with uncoated PEEK.[28,41]

PEEK Allergy

Katzer et al[42] investigated mutagenicity and cytotoxicity of PEEK in an animal study. There was no evidence of mutagenicity and cytotoxicity on the human organism from PEEK braid, its ethanol, or chloroform extracts under the appropriate conditions in their report. Similarly, carbon fiber–reinforced PEEK did not show any adverse reactions.[42] In another study, Wenz et al[43] investigated the biocompatibility of PEEK focusing on cytotoxicity. There was also no evidence of cytotoxicity, mutagenicity, carcinogenicity, and immunogenicity of PEEK and its composites in a bulk form.[29] Another research group evaluated the influence of PEEK-Optima, ultrahigh-molecular weight polyethylene (UHMWPE) and cross-linked UHMWPE (X-UHMWPE) with 3 different particle sizes (0.7, 2, and 10 μm) at the dose of 20 particles per cell on monocytes and macrophages after 24 and 48 hours. Different assays and cytokine analysis (interleukin [IL]-1b, IL-6, IL-8, monocyte chemotactic protein 1 (MCP-1), and tumor necrosis factor [TNF]-α) did not present a significant difference on viability or proliferation between the 3 different materials. PEEK-Optima showed less cytotoxicity response compared with UHMWPE and X-UHMWPE, after 24 and 48 hours. The highest reaction was observed at particle size of 0.7 μm. Particles of X-UHMWPE presented significantly more IL-1b, IL-6, MCP-1, and TNF-α at 24 hours.[44] This literature review revealed 7 animal studies and 1 clinical study using HPPs.

Animal Studies With PEEK

Osseointegration and infection. Cook and Rust-Dawicki[37] investigated the interface attachment strength between PEEK and the unicortical bone in 4 mongrel dogs (Table 3). They placed overall 40 titanium-coated and uncoated cylindrical implants of PEEK in unicortical site of the femurs.[37] The implants were examined mechanically and histologically after killing the animals. Bone contact, porosity, bone in-growth, inflammatory response, and mode of failure after 4 and 8 weeks were the parameters of interest. The uncoated implants showed significantly higher interfacial shear strength after 4 weeks. There was no difference between the uncoated and coated implants after 8 weeks. However, the titanium-coated materials presented

Table 3. Summary of Findings of Animal Studies Using HPP PEEK as an Implant Material

Author Group	Objective	Animal	Implant Material	Manufacturer	Results	Conclusion
Cook et al[37]	To measure attachment strength and bone contact	Mongrel dogs	Titanium-coated and titanium-uncoated PEEK	—	Significantly higher interface attachment of uncoated implants after 4 wk; no difference after 8 wk	After 8 wk, there was no difference in bone contact
Rohner et al[38]	To compare the healing, mechanical and initial vascular disturbance with SP and LCP	Sheep	SP: CF reinforced PEEK (62% CF and 38% PEEK) LCP: 7-hole titanium plate (4.5)	SP: Icotec AG, Altstätten, Switzerland LCP: Synthes, GmbH & Co KG, Umkirch, Germany	The strength for the SP group was −13.93% and for the LCP group −7.49%; the stiffness showed similar values in both groups (SP group: −24.44%, LCP group: −27.08%); there was initial vascular disturbance after plate insertion but no significant disturbance in periostal circulation	CF-PEEK seems to be a considerable replacement material for metallic implants for bone fractures
Toth et al[36]	The radiolucent PEEK-threaded interbody cages that were filled with autograft (n = 7) or rhBMP-2 (n = 6) on an absorbable collagen sponge were evaluated	Sheep	PEEK, InFuse bone graft substitute: rhBMP-2	PEEK: PEEK-Optima, Invibio, Greenville, SC InFuse bone graft substitute: Medtronic Sofamor Danek, Memphis, TM rhBMP-2: Wyeth Research, Cambridge, MA	There was no device degradation or wear debris at the PEEK cages; mild chronic inflammation with few macrophages around the peri-implant tissue was demonstrated	Biomaterial PEEK was suggested to be a valuable material for interbody fusion cages in traumatic and orthopedic surgery
Nakahara et al[46]	To compare CF-reinforced PEEK (CFR/PEEK) cups and stems with HA coatings for cementless hip prostheses and without HA for cement fixation in 16 sheep (radiographically and histologically); each animal obtained a unilateral total hip replacement	Sheeps	CFR/PEEK composites (50% and 65% volumetric fraction), PEEK compound (30% weight fraction), and Ti6Al4V	—	All cases with titanium stem and 2 cases with CFR-PEEK presented bone ongrowth fixation of the remaining animals; osteopenia was observed in 3 of 5 cases of the titanium stem but not in the CFR-PEEK cases; the results were evaluated radiographically and histologically	The radiolucency of CFR/PEEK gives the possibility to assay the osseointegration by using CT; bone resorption was reduced due to lower stiffness of this material

(continued on next page)

Table 3. (Continued)

Author Group	Objective	Animal	Implant Material	Manufacturer	Results	Conclusion
Webster et al[39]	To investigate the occurrence of bacterial infection in silicon nitride (Si_3N_4) compared with PEEK and titanium implants	Wistar rats	Si_3N_4, ASMT grade 4 titanium and PEEK Optima	Si_3N_4: Amedica Corp., Salt Lake City, UT	About 64% of Si_3N_4, 24% of PEEK, and 36% of titanium showed new bone formation with absence of bacteria injection 3 mo after surgery	Si_3N_4 presented significantly better new bone formation and resistance to bacterial infection in contrast to titanium and PEEK
				ASMT grade 4 titanium: Fisher Scientific, Continental Steel & Tube Co., Fort Lauderdale, FL PEEK Optima: Invibio Thornton Cleveleys, Lancashire, United Kingdom	Bone formation with presence of bacteria was Si_3N_4: 41%, titanium: 26%, and PEEK: 21%	
Wu et al[40]	To evaluate the bioactivity of nano-TiO_2 (n-TiO_2) and PEEK that were fabricated with amounts of n-TiO_2 and PEEK powder	Beagle dogs	PEEK powder, n-TiO_2/PEEK nanocomposites	PEEK powder: Victrex, Lancashire, United Kingdom n-TiO_2/PEEK nanocomposites: Key Laboratory for Ultrafine Material of Ministry of Education, School of Materials Science and Engineering, East China University of Science and Technology, Shanghai	There was more cell attachment at the rough n-TiO_2/PEEK, whereas the smooth PEEK presented the lowest optical density value; 2 implants of PEEK and n-TiO_2/PEEK were placed on each tibia of the animals; PEEK showed almost half of the percent bone volume value compared with n-TiO_2/PEEK	n-TiO_2 improves the bioactivity of PEEK, thus it is essential; this material may be a considerable alternative to titanium
Nakahara et al[34]	To compare the bone ongrowth fixation of CFR-PEEK cups and stems with surface coating with HA (cementless) and cups and stems without coating (cemented fixation)	Sheep	CFR/PEEK composites (50% and 65% volumetric fraction), PEEK compound (30% weight fraction), Ti6Al4V and CoCr	—	Good performance of cementless and cemented CFR/PEEK stems fixation; cup fixation (cementless and cemented) was very difficult	A considerable cementless fixation can be obtained with the application of the HA-coating CFR/PEEK

CF indicates carbon fiber.

Table 4. Summary of Findings of Clinical Studies Using HPP PEEK as an Implant Material

Author Group	Objective	Implant Material	Manufacturer	Results	Conclusion
Chou et al[45]	To compare the fusion rates of different implant materials	Nonthreaded titanium cage containing a biphasic calicum phosphate ceramic triosite, 40% β-tricalcium phosphate, and 60% HA; PEEK cage interbody fusion containing triosite	Nonthreaded titanium cage: Zimmer, Berlin, Germany PEEK cage: Solis; Stryker, Allendale, NJ	There were 2 radiographically fusion rates after 6 and 12 mo; after 6 mo—group A: 37.21%, group B: 93.3%, and group C: 84.85%; after 12 mo—group A: 46.51%, group B and C: 100%	PEEK cages showed a similar fusion rates compared with autogenous tricortical bone graft but it may have fewer complications on the donor site

significantly higher percentage of bone contact at both time-points.[37]

Nakahara et al[34] pursued a similar approach. They compared CFR/PEEK cups and stems with HA coatings for cementless hip prostheses and without HA for cement fixation in 16 sheep. Each animal received a unilateral total hip replacement. The follow-up was up to 52 weeks. Overall, 5 cementless cups and stems and 6 cemented cups and stems were radiographically and histologically investigated. Five sheep were excluded because of early complications. They indicated that cementless and cemented CFR/PEEK fixation presented a good stability in the bone. A difference was found in the cup fixation because the attachment was difficult in both types. In 2 cases, the bone ongrowth in the cementless cups were observed initially. In another study of Nakahara et al,[46] they compared the bone ongrowth fixation of surface roughened, bioactive and uncemented CFR-PEEK stems, and titanium (Ti6Al4V) stems in 12 bovines. Each animal received a unilateral hemiarthroplasty of the hip. The follow-up period was 12 months. Titanium stems were applied as a control. Three bovines limped and were killed within the first 4 weeks. All cases with titanium stem and 2 cases with CFR-PEEK presented bone ongrowth fixation of the remaining animals. Osteopenia was observed in 3 of 5 cases of the titanium stem but not in the CFR-PEEK cases.

Besides the osteointegration, the incidence of bacterial infection is an important aspect in implantology. Webster et al[39] investigated this aspect in silicon nitride (Si_3N_4) and the results with PEEK and titanium implants. All 3 different materials were implanted in calvarial defects of 96 rats following of injection of 1×10^4 *Staphylococcus epidermidis* and saline at the control group. Four rats were killed and examined for the quantity of bone formation and presence of bacteria after 3, 7, and 14 days and 3 months. About 64% of Si_3N_4, 24% of PEEK, and 36% of titanium showed a new bone formation with absence of bacteria injection 3 months after surgery. Si_3N_4 demonstrated 41%, titanium 26%, and PEEK 21% bone formation in the presence of bacteria. Briefly, Si_3N_4 presented a significantly better new bone formation and resistance to bacterial infection in contrast to titanium and PEEK.

Wu et al[40] evaluated the bioactivity of different amounts of nano-TiO_2 (n-TiO_2) and PEEK powder. The resulting powder mixture (n-TiO_2/PEEK) was placed in a specially manufactured mould disk (15 × 2 mm) for physical and chemical characterization and *in vitro* testing and cylindrical implants (4 × 7 mm) for *in vivo* testing. PEEK acted as a control. Scanning, transmission electron microscopy, and x-ray photoelectron spectroscopy were used to analyze the surface and dispersion in the composites. There was more cell attachment at the rough n-TiO_2/PEEK, whereas the smooth PEEK presented significantly lower optical density. The authors used 3 beagle dogs for the *in vivo* examination. Two implants of PEEK and n-TiO_2/PEEK were placed on each tibia of the animals. The dogs were killed after 4 weeks. PEEK showed almost half of the percent bone volume value compared with n-TiO_2/PEEK ($P < 0.05$).[40]

Biocompatibility

In the orthopedic spine surgery, the use of PEEK is often described. In an animal study with 13 sheep, Toth et al[36] evaluated a radiolucent PEEK-threaded interbody cages, which was filled with autograft ($n = 7$) or rhBMP-2 ($n = 6$) on an absorbable collagen sponge. The fusion was investigated with blinded radiographic, biomechanic, histologic, and statistical procedures after 6 months. The authors observed no device degradation or wear debris at the PEEK cages. Only a mild chronic inflammation with few macrophages around the peri-implant tissue was demonstrated.

Mechanical Properties

Rohner et al[38] compared the performance of CFR/PEEK radiolucent plate (snake plate [SP]) with high stiffness and fixed-angle converging screws with a 7-hole titanium locking compression plate (LCP). They used 18 sheep, where an osteotomy in a tibia was performed and stabilized with an SP ($n = 6$) or an LCP ($n = 6$). They measured the callus dimension with x-ray in each group after 0, 2, 4, 6, and 8 weeks. The animals were killed after 8 weeks, and they measured in pairs the torsion to determine strength and stiffness in the osteomized and contralateral tibiae. There was no significant difference between the osteomized and nonosteomized tibia. The authors calculated the median value for relative reduction of strength (100 × [operated – contralateral]/contralateral). The strength for the SP group was –13.93% and –7.49% for the LCP group. The stiffness showed similar values in both groups (SP group: –24.44% and LCP group: –27.08%). Rohner et al[38] used the 6 remaining sheep for a second experiment. They evaluated the initial vascular disturbance after plate insertion. In this experiment, there was also no significant disturbance in periosteal circulation.

Clinical Studies

Osseointegration. Chou et al[45] investigated 55 patients who received a segmental anterior discectomy with a follow-up period of up to 12 months. They formed 3 groups: group A (n = 27) received implants of a titanium cage packed with biphasic calcium phosphate ceramic, group B (n = 9) was operated with PEEK cages containing triosite, and group C received autogenous tricortical iliac crest bone graft. There were 2 radiographically fusion rates after 6 and 12 months (after 6 months—group A: 37.21%, group B: 93.3%, and group C: 84.85%; after 12 months—group A: 46.51%, groups B and C 100% fusion rates) (Table 4). There was no randomized control clinical trial found at the time of this review.

DISCUSSION

In this review, only 7 animal studies and 1 clinical study could provide information on the question whether PEEK material could be an alternative to Ti implants. Although Ti shows many advantages and is a well-tolerated metal, investigations continue to eliminate metals from dentistry and replace them with more inert nonmetallic materials.

From the biomechanical point of view, Rohner et al[38] investigated the stiffness and strength of radiolucent CFR-PEEK plate and a titanium plate for osteosynthesis in a sheep model with the outcome that both materials presented similar mechanical properties. This study also indicated that CFR-PEEK is not only an excellent osteosynthesis material but it also does not produce artifacts in radiographical examinations. PEEK having Young modulus with 10–30 GPa closer to human bone may have better implications in less marginal bone resorption and osteolysis as opposed to titanium and zirconia.

Investigation in spinal surgery using PEEK[28,47] and dental implants[31,37] indicated high biocompatibility and no evidence of cytotoxicity, mutagenicity, carcinogenicity, and immunogenicity.[28] The animal study by Toth et al[36] described a good biocompatibility without device degradation and wear debris of the PEEK cages. Although the follow-up time of the experiment was relatively short, authors claimed that there was an indication of PEEK being a substitute for titanium-based implants, considering the radiographic, biomechanical, and histological results.

Currently, bone nails that are used as osteosynthesis material for bone fractures are made of PEEK. However, this review did not find its application in dental implantology to qualify the material as an oral implant. Any releasing of ions or debris of PEEK is not known. Nanometer-sized particles generated as a consequence of wearing of the metal implant surface are potential factors for osteolysis and may influence of the implant longevity.[25] These aspects need further investigation with HPPs.

According to the results of animal studies, excellent osseointegration of coated carbon fiber reinforced PEEK[34,37] were comparable with titanium.[46] This indicates that potential coatings may be needed for CFR/PEEK to make it a realistic alternative to titanium for medical and dental implants. Nakahara et al[46] could show in their study that no osteopenia has occurred in CFR-PEEK stems compared with the titanium stems. This may be a further advantage of this HPP. In bacterial infection, PEEK has a less biofilm resistance effect compared with silicon nitride (Si_3N_4) and titanium.[39] This suggests that PEEK implant with a bacterial infection would need an antibiotic therapy over a long time, which may have a negative consequence of the general health concerning of the antibiotic resistance difficulty.

It could be easily conceivable that not only implants consist of HPP but also the abutments. In a recent study, the influence of titanium and polymer abutments had favorable effect on the soft and hard tissues. They observed an effect of bone and soft tissue level.[48] However, there would not be any mechanical and chemical interactions between 2 different materials if implant and its abutment consisted of the same chemical structure.

HPP could play a role not only for medical and dental implants but also in the reconstructive surgery. Von Wilmowsky et al[49] examined the influence of laser sintered PEEK with incorporated nano-sized carbon black, β-tricalcium phosphate and bioactive glass 45S5 on human osteoblasts (hFOB 1.19). The highest proliferation rate of osteoblasts was observed the bioactive glass containing sintered PEEK at day 7 (OD 1.76 ± 0.22) and at day 14 (OD 3.75 ± 0.31) compared with pure PEEK as the control group. These results presented that laser sintered PEEK would be a reasonable alternative to bone substitute for reconstructive surgery.[49] Another research group coated the surface of PEEK with titanium by using an electron beam with the objective of evaluating biocompatibility and adhesion to bone tissue. The study showed a considerable higher bone contact of titanium-coated PEEK compared with pure PEEK.[50] Furthermore, there is need for more investigations concerning contact stress and wear of HPP materials. That would lead to a better understanding of the mechanical characterization.[51] Although PEEK seemed to have excellent properties and be considered as an alternative material to titanium, cobalt-chrome and other materials, more research is required.

CONCLUSIONS

Metallic implant materials, and in particular, titanium and its alloys, continue to be the materials of choice for medical and dental implantology because of their biocompatibility, resistance to corrosion, and mechanical properties. Despite their advantages, these materials implicate some issues such as osteolysis followed by implant failure, scattered radiation, occasional hypersensitivity, allergy, and possibly surface degradation related to peri-implantitis. A nonmetallic material such as HPP PEEK seems to have favorable properties. Yet, the numbers of experimental, animal, and clinical studies were limited to make conclusions for their medical and dental utilization.

DISCLOSURE

The authors claim to have no financial interest, either directly or indirectly, in the products or information listed in the article.

ACKNOWLEDGMENTS

Author contributions: M. Özcan designed the study. M. G. Wiesli and M. Özcan performed experiments and wrote the paper.

REFERENCES

1. Lautenschlager EP, Monaghan P. Titanium and titanium alloys as dental materials. *Int Dent J.* 1993;43:245–253.
2. Renouard F, Nisand D. Impact of implant length and diameter on survival rates. *Clin Oral Implants Res.* 2006;17:35–51.
3. Long M, Rack HJ. Titanium alloys in total joint replacement—A materials science perspective. *Biomaterials*. 1998;19:1621–1639.
4. Milosev I, Metikos-Huković M, Strehblow HH. Passive film on orthopaedic TiAlV alloy formed in physiological solution investigated by X-ray photoelectron spectroscopy. *Biomaterials*. 2000;21:2103–2113.
5. Mouhyi J, Dohan Ehrenfest DM, Albrektsson T. The peri-implantitis: Implant surfaces, microstructure, and physicochemical aspects. *Clin Implant Dent Relat Res.* 2012;14:170–183.
6. Dorr LD, Bloebaum R, Emmanual J, et al. Histologic, biochemical, and ion analysis of tissue and fluids retrieved during total hip arthroplasty. *Clin Orthop Relat Res.* 1990;261:82–95.
7. Poggio CE. Plasmacytoma of the mandible associated with a dental implant failure: A clinical report. *Clin Oral Implants Res.* 2007;18:540–543.
8. Wheeler SL. Eight-year clinical retrospective study of titanium plasma-sprayed and hydroxyapatite-coated cylinder implants. *Int J Oral Maxillofac Implants.* 1996;11:340–350.
9. Albrektsson T, Wennerberg A. Oral implant surfaces: Part 1—Review focusing on topographic and chemical properties of different surfaces and in vivo responses to them. *Int J Prosthodont.* 2004;17:536–543.
10. Zhao L, Chu PK, Zhang Y, et al. Antibacterial coatings on titanium implants. *J Biomed Mater Res B Appl Biomater.* 2009;91:470–480.
11. Hetrick EM, Schoenfisch MH. Reducing implant-related infections: Active release strategies. *Chem Soc Rev.* 2006;35:780–789.
12. da Silva EP, De Martinis EC. Current knowledge and perspectives on biofilm formation: The case of *Listeria monocytogenes*. *Appl Microbiol Biotechnol.* 2013;97:957–968.
13. Römling U, Balsalobre C. Biofilm infections, their resilience to therapy and innovative treatment strategies. *J Intern Med.* 2012;272:541–561.
14. Schalock PC, Menné T, Johansen JD, et al. Hypersensitivity reactions to metallic implants—Diagnostic algorithm and suggested patch test series for clinical use. *Contact Dermatitis.* 2012;66:4–19.
15. Ozen J, Dirican B, Oysul K, et al. Dosimetric evaluation of the effect of dental implants in head and neck radiotherapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2005;99:743–747.
16. Friedrich RE, Todorovic M, Krüll A. Simulation of scattering effects of irradiation on surroundings using the example of titanium dental implants: A Monte Carlo approach. *Anticancer Res.* 2010;30:1727–1730.
17. Lesmes D, Laster Z. Innovations in dental implant design for current therapy. *Oral Maxillofac Surg Clin North Am.* 2011;23:193–200.
18. Nakamura K, Kanno T, Milleding P, et al. Zirconia as a dental implant abutment material: A systematic review. *Int J Prosthodont.* 2010;23:299–309.
19. Özkurt Z, Kazazoğlu E. Zirconia dental implants: A literature review. *J Oral Implantol.* 2011;37:367–376.
20. Akagi K, Okamoto Y, Matsuura T, et al. Properties of test metal ceramic titanium alloys. *J Prosthet Dent.* 1992;68:462–467.
21. Kelly JR, Denry I. Stabilized zirconia as a structural ceramic: An overview. *Dent Mater.* 2008;24:289–298.
22. Zartman KC, Berlet GC, Hyer CF, et al. Combining dissimilar metals in orthopaedic implants: Revisited. *Foot Ankle Spec.* 2011;4:318–323.
23. Schmalzried TP, Jasty M, Harris WH. Periprosthetic bone loss in total hip arthroplasty. Polyethylene wear debris and the concept of the effective joint space. *J Bone Joint Surg Am.* 1992;74:849–863.
24. Weber BG. Experience with the Metasul total hip bearing system. *Clin Orthop Relat Res.* 1996;329:S69–S77.
25. Delaunay C, Petit I, Learmonth ID, et al. Metal-on-metal bearings total hip arthroplasty: The cobalt and chromium ions release concern. *Orthop Traumatol Surg Res.* 2010;96:894–904.
26. Barry J, Lavigne M, Vendittoli PA. Evaluation of the method for analyzing chromium, cobalt and titanium ion levels in the blood following hip replacement with a metal-on-metal prosthesis. *J Anal Toxicol.* 2013;37:90–96.
27. Eschbach L. Nonresorbable polymers in bone surgery. *Injury*. 2000;31:22–27.
28. Kurtz SM, Devine JN. PEEK biomaterials in trauma, orthopedic, and spinal implants. *Biomaterials*. 2007;28:4845–4869.
29. Kurtz SM. *PEEK Biomaterials Handbook*. Waltham, MA: Elsevier Science; 2012:30–31.
30. Skinner HB. Composite technology for total hip arthroplasty. *Clin Orthop Relat Res.* 1988;235:224–236.
31. Lee WT, Koak JY, Lim YJ, et al. Stress shielding and fatigue limits of poly-ether-ether-ketone dental implants. *J Biomed Mater Res B Appl Biomater.* 2012;100:1044–1052.
32. Devine DM, Hahn J, Richards RG, et al. Coating of carbon fiber-reinforced polyetheretherketone implants with titanium to improve bone apposition. *J Biomed Mater Res B Appl Biomater.* 2013;101:591–598.
33. Grupp TM, Giurea A, Miehlke RK, et al. Biotribology of a new bearing material combination in a rotating hinge knee articulation. *Acta Biomater.* 2013;9:7054–7063.
34. Nakahara I, Takao M, Bandoh S, et al. In vivo implant fixation of carbon fiber-reinforced PEEK hip prostheses in an ovine model. *J Orthop Res.* 2013;31:485–492.
35. Clarke IC, Donaldson T, Bowsher JG, et al. Current concepts of metal-on-metal hip resurfacing. *Orthop Clin North Am.* 2005;36:143–162.
36. Toth JM, Wang M, Estes BT, et al. Polyetheretherketone as a biomaterial for spinal applications. *Biomaterials*. 2006;27:324–334.
37. Cook SD, Rust-Dawicki AM. Preliminary evaluation of titanium-coated PEEK dental implants. *J Oral Implantol.* 1995;21:176–181.
38. Rohner B, Wieling R, Magerl F, et al. Performance of a composite flow

moulded carbon fibre reinforced osteosynthesis plate. *Vet Comp Orthop Traumatol.* 2005;18:175–182.

39. Webster TJ, Patel AA, Rahaman MN, et al. Anti-infective and osteointegration properties of silicon nitride, poly(ether ether ketone), and titanium implants. *Acta Biomater.* 2012;8:4447–4454.

40. Wu X, Liu X, Wei J, et al. Nano-TiO2/PEEK bioactive composite as a bone substitute material: In vitro and in vivo studies. *Int J Nanomedicine.* 2012;7:1215–1225.

41. Rabiei A, Sandukas S. Processing and evaluation of bioactive coatings on polymeric implants. *J Biomed Mater Res A.* 2013;101:2621–2629.

42. Katzer A, Marquardt H, Westendorf J, et al. Polyetheretherketone-cytotoxicity and mutagenicity in vitro. *Biomaterials*. 2002;23:1749–1759.

43. Wenz LM, Merritt K, Brown SA, et al. In vitro biocompatibility of polyetheretherketone and polysulfone composites. *J Biomed Mater Res.* 1990;24:207–215.

44. Hallab NJ, McAllister K, Brady M, et al. Macrophage reactivity to different polymers demonstrates particle size- and material-specific reactivity: PEEK-optima particles versus UHMWPE particles in the submicron, micron, and 10 micron size ranges. *J Biomed Mater Res B Appl Biomater.* 2012;100B:480–492.

45. Chou YC, Chen DC, Hsieh WA, et al. Efficacy of anterior cervical fusion: Comparison of titanium cages, polyetheretherketone (PEEK) cages and autogenous bone grafts. *J Clin Neurosci.* 2008;15:1240–1245.

46. Nakahara I, Takao M, Bandoh S, et al. Novel surface modifications of carbon fiber-reinforced polyetheretherketone hip stem in an ovine model. *Artif Organs.* 2012;36:62–70.

47. Niu CC, Liao JC, Chen WJ, et al. Outcomes of interbody fusion cages used in 1 and 2-levels anterior cervical discectomy and fusion: Titanium cages versus polyetheretherketone (PEEK) cages. *J Spinal Disord Tech.* 2010;23:310–316.

48. Koutouzis T, Richardson J, Lundgren T. Comparative soft and hard tissue responses to titanium and polymer healing abutments. *J Oral Implantol.* 2011;37:174–182.

49. von Wilmowsky C, Vairaktaris E, Pohle D, et al. Effects of bioactive glass and beta-TCP containing three-dimensional laser sintered polyetheretherketone composites on osteoblasts in vitro. *J Biomed Mater Res A.* 2008;87:896–902.

50. Han CM, Lee EJ, Kim HE, et al. The electron beam deposition of titanium on polyetheretherketone (PEEK) and the resulting enhanced biological properties. *Biomaterials*. 2010;31:3465–3470.

51. Albert K, Schledjewski R, Harbaugh M, et al. Characterization of wear in composite material orthopaedic implants. Part II: The implant/bone interface. *Biomed Mater Eng.* 1994;4:199–211.